AMENDMENT TO THE DRAWINGS

Enclosed herewith please find a set of replacement drawings, wherein Fig. 5 - Fig. 9 have been amended to include sequence identifiers.

REMARKS

Applicant acknowledges that claims 11-16 have been withdrawn resulting from an election of SEQ ID NO: 2 (with Ser at position 17) with claims 1-10 and 17-27 under examination.

In view of the submission of an amended sequence listing, the objection to the application as not being in compliance with the sequence rules 37 CFR 1.821-1.825 should be withdrawn.

The rejection of claims 17, 20 and 25 under 35 USC 112, first paragraph is respectfully traversed. Applicant has filed a Declaration for the deposited materials stating that the biological materials have been deposited under the Budapest Treaty and have been deposited under conditions that assure access during pendency of the patent application pursuant to 37 CFR 1.14 and 35 USC 122, and that the materials will be maintained viable for at least 30 years after deposit or life of the patent following grant.

Accordingly, this rejection should be withdrawn.

35 USC § 102 Rejection

The rejection of claims 1-8, 18-19, 21-24 and 26-27 under 35 USC 102(a) as being anticipated by Rosendahl et al. and the rejection under 35 USC 102(b) in view of Kuga et al., is respectfully traversed.

In view of the submission herewith of a certified English translation of Korean Patent Application No. 1999-27418, it is believed that the Examiner's

rejection under 35 U.S.C. 102(e) of claims 1-10, 18, 19, 21-24, 26 and 27 as being anticipated by Rosendahl et al., is no longer applicable and should be withdrawn.

The present invention as defined in claim 1, is directed to a modified human granulocyte-colony stimulating factor (hG-CSF) characterized in that at least one of the 1st, 2nd, 3rd and 17th amino acids of wild-type hG-CSF (SEQ ID NO: 2) is replaced by other amino acid(s) and that the modified hG-CSF has no methionie residue at the N-terminus thereof.

The modified hG-CSF of the present invention had advantages in that the biological activity of the wild-type is retained and that it can be efficiently produced by a microorganism in the form of a soluble modified hG-CSF without a methionie residue at the N-terminus thereof, the form expressed in human cells, when an appropriate secretory signal peptide is employed in preparation of its expression vector.

Kuga et al. relates to a modified hG-CSF which teaches an expression vector, pCFAB5, comprising a nucleotide sequence encoding a modified hG-CSF containing a methionie residue attached at the N-terminus thereof because pCFAB5 is an *E.coli* expression vector.

Many articles and patents, including Kuga et al. cited by the Examiner, deal with modified hG-CSF. However, the modified hG-CSFs disclosed therein are in the form of either a glycosylated G-CSF having no Met residue at the N-terminus prepared by employing the eukaryotic cell expression system or a non-

glycosylated G-CSF containing an N-terminal Met residue prepared by employing the prokaryotic cell (e.g., *E.coli*) expression system.

Firstly, since it has been known that the glycosylation of hG-CSF is not necessary for the activity of hG-CSF (see Lawrence, M. et al., Science, 232, 61(1986)), there have been attempts to efficiently produce a modified hG-CSF by employing a microorganism, e.g., *E. coli.* However, hG-CSFs thus produced have a methionine residue attached at the N-terminus thereof due to the ATG initiation codon employed in the microorganism, and such an additional methionine residue has been reported to cause undesirable immune responses in human body when the modified hG-CSF is administered thereto (see European Patent Publication No. 256,843).

Further, most of the methionine-containing hG-CSFs produced in *E. coli* are deposited in the cells as insoluble inclusion bodies, and they must be converted to an active form through a refolding process, at a significant loss of yield.

The modified hG-CSF of the present invention has an amino acid sequence obtained by replacing at least one of the 1st, 2nd, 3rd and 17th amino acids of wild-type hG-CSF sequence and has no N-terminal methionine residue, as shown in SEQ ID NO: 2.

For the above reasons, the modified hG-CSF of the subject invention differs from the modified hG-CSF taught in Kuga et al. notwithstanding the fact that

both may represent modified hG-CSFs in which the17th amino acid is replaced with Ser.

Accordingly, Kuga et al. fails to anticipate the critical feature of the present invention and the rejection under 35 USC 102 should be withdrawn.

35 USC § 103 rejection

The modified hG-CSF of the present invention contains no N-terminal Met residue and can be efficiently produced employing a microorganism (e.g., *E.coli*) together with an appropriate secretory signal peptide, because fusion proteins prepared by adding a signal peptide to N-terminus of the inventive modified hG-CSF are predominantly secreted to the periplasm when expressed in *E.coli*, resulting in the N-terminal signal peptide being removed once passed through the cell membrane (see Table 1 on page 19 of the subject application).

However, Kuga et al. merely teach an *E.coli* expression vector comprising a nucleotide sequence encoding a modified hG-CSF wherein 17th amino acid is Ser, and fails to show any data or statement suggesting the characteristic secretary effect of the present invention.

It is acknowledged that Builder et al. discloses the use of the *E.coli* thermoresistant enterotoxin II.

However, one skilled in the art could not anticipate, predict or expect from the teaching of Kuga et al., even if combined with the use of the *E.coli*

thermoresistant enterotoxin II disclosed in Builder et al., that a modified hG-CSF (especially, [Ser17] hG-CSF) can be successfully produced from prokaryotic transformants without a Met residue when an appropriate secretory signal peptide is employed in preparation of its expression vector.

For all of the above reasons, no basis exists to support a rejection over Kuga et al taken alone or in combination with Builder et al based upon obviousness under 35 USC 103 without applying hindsight from reading the subject application.

Reconsideration and allowance of claims 1-10 and 17-27 is respectfully solicited.

Respectfully submitted
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Dated: February 15, 2007

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CERTIFICATE OF MAILING

I hereby certify that this *Amendment w/attachments* is being deposited with the United States Postal Service via First Class Mail addressed to: Mail Stop AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on February 15, 2007.

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Audrey de Souza

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